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Metabolic Syndrome: Impact of Dietary Therapy

Suzanne Fouad Soliman

Abstract

Metabolic syndrome refers to the coexistence of insulin resistance (IR) with several risk factors, including abdominal obesity, atherogenic dyslipidemia, and hypertension, which is usually complicated by cardiovascular and/or cerebrovascular diseases. This clustering of risk factors suggests that they are interrelated and not independent of one another and that they share underlying mechanisms, mediators, and pathways. Its prevalence exceeds 40% of those over 40, and it has recently been diagnosed in adolescents and even children. Metabolic syndrome is a pro-inflammatory prothrombotic state with determination of elevated level of cytokines, acute phase reactants, fibrinogen, and plasminogen activator inhibitor-1. A comprehensive definition of metabolic syndrome and its pathogenesis would facilitate research into its causes and disease pathophysiology linking the components of metabolic syndrome with the increased risk of cardiovascular diseases. The management to mitigate these underlying risk factors constitutes a first-line intervention; dietary therapy of metabolic syndrome includes lifestyle modification, hypocaloric diet, and consumption of functional food. Healthy food quantity and time of consumption help restore the normal metabolic profiles. Hopefully, this will lead to new insights into facilitating epidemiological and clinical studies of pharmacological, lifestyle, and preventive treatment approaches.

Keywords: metabolic syndrome, circadian rhythm, insulin resistance, sleep, functional foods, lifestyle modification, hypocaloric diets

1. Introduction

The prevalence of metabolic syndrome (MetS) worldwide varies between 10 and 84% depending on the age, gender, and race of the population [1]. The International Diabetes Federation estimates that one-quarter of the world's population has MetS [2]. Although the prevalence of MetS varies throughout the world and depends on the particular health organization used for its definition, it is clear that the number of people complaining about this syndrome has globally risen [3], due to a more sedentary life, the increase in the number of smokers, unhealthy dietary habits, and the increase in stress [4].

MetS is a cluster of metabolic disturbances that tend to coexist. Different health organizations have suggested diverse definitions for MetS. However, it is clear that MetS is a clinical entity of substantial heterogeneity, commonly represented by the combination of central abdominal obesity, hyperglycemia, dyslipidemia, and/or hypertension [5, 6].

In 1994, the World Health Organization [7] defined MetS as the presence of one of the following: type II diabetes mellitus, insulin resistance, or impaired glucose tolerance, plus at least two of the following—triglycerides (TG) ≥ 150 mg/dL (≥ 1.7 mmol/L) and/or HDL cholesterol < 40 mg/dL (≤ 0.9 mmol/L) (males) and < 50 mg/dL (≤ 1.0 mmol/L) (females); urine albumin excretion > 20 g/min or albumin/creatinine ratio > 30 mg/g; systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or a prescription of hypertension; and central obesity, waist circumference (WC) ≥ 102 cm (males) and ≥ 88 cm (females), waist/hip ratio > 0.90 (males) and > 0.85 (females), and/or body mass index (BMI) > 30 kg/m² [8].

The International Diabetes Federation defined MetS as encompassing at least three of the following five conditions: (1) male waist circumference ≥ 94 cm and female waist circumference ≥ 80 cm; (2) fasting glucose level ≥ 100 mg/dL; (3) SBP ≥ 130 and/or DBP ≥ 85 mmHg or under medical treatment for hypertension; (4) TG ≥ 150 mg/dL or ≥ 1.7 mmol/L or prescribed pharmacological treatment for hypertriglyceridemia; or (5) male HDL cholesterol < 40 mg/dL and female HDL cholesterol < 50 mg/dL [9].

Other markers used for diagnosis of metabolic syndrome include high-sensitivity C-reactive protein concentrations (hs-CRP) ≥ 3 mg/dL [10], uric acid [11], fibrinogen [12], plasminogen activator inhibitor-1 [13, 14], increased homocysteine [15, 16], and decreased adiponectin [17]. Fibrinogen, plasminogen activator inhibitor-1, cytokines, and hs-CRP protein are often elevated in patients with MetS, resulting in a prothrombotic and pro-inflammatory state. These biomarkers are not routinely evaluated in clinical practice. hs-CRP ≥ 3 mg/dL indicates a state of inflammation and a higher risk of atherosclerotic cardiovascular disease (ASCVD).

2. Characterization and risk assessment

MetS is a link between visceral adiposity, insulin resistance, inflammation, and endothelial dysfunctions [18, 19].

2.1 Visceral adiposity

Visceral adiposity (abdominal fats close to the visceral organs) leads to an imbalance in the secretion of pro-inflammatory and anti-inflammatory factors. Adipocytes produce pro-inflammatory factors in excess, such as IL-6, IL-10, TNF- α , and hs-CRP. These cytokines block the intracellular insulin signaling pathways. Moreover, the adipose tissue inhibits adiponectin [20, 21].

2.2 Insulin resistance

Insulin resistance (IR) rises with increased waist circumference or body fat and is not related to the body mass index. IR results in the diversion of excess non-esterified fatty acids from lipid-overloaded IR muscles to the hepatic cells, resulting in nonalcoholic fatty liver disease and atherogenic dyslipidemia. IR predisposes to glucose intolerance, which may be aggravated by increased hepatic gluconeogenesis with an IR liver [22].

2.3 Pro-inflammatory condition

Inflammation is a response of the immune system to injury. It is a mechanism in the pathogenesis and progression of obesity-related medical disorders and the link between adiposity, IR, MetS, and cardiovascular disease [23]. Oxidative stress is a

condition in which there is an imbalance between the prooxidants and antioxidants in the body [24]. It plays a key role in the pathogenesis of atherosclerosis through different mechanisms such as the oxidation of LDL-c particles [24, 25] or the impairment of HDL-c functions [26].

2.4 High blood pressure

Hypertension is defined as a resting SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or the use of medical prescription to lower blood pressure [27]. Activation of the sympathetic nervous system together with the activation of the renin-angiotensin system by the hyperglycemia and antinatriuretic effect of insulin, in addition to some obese people being salt sensitive, contributes to the development of hypertension. It is identified as a major cardiovascular and renal risk factor related to heart disease, myocardial infarction, cerebrovascular stroke, and vascular diseases [28].

2.5 Circadian rhythm disruption

Over the last two decades, a deeper comprehension of the molecular mechanisms that control the biological clock and circadian rhythm has been achieved. The 2017 Nobel Prize in Physiology was awarded to Jeffrey C. Hall, Michael Rosbash, and Michael Young for their work on circadian rhythms [29, 30]. There are interconnections between the circadian rhythm and endocrine homeostasis. Biological clock disruption was in fact associated to an increased incidence of metabolic and endocrine diseases. Irregular rhythms have been linked to various chronic health conditions, such as sleep disorders, obesity, type II diabetes mellitus, hypertension, gastrointestinal motility diseases, depression, cardiac diseases, cognitive dysfunction, bipolar disorder, and seasonal affective disorder [31]. The master clock in mammals that controls circadian rhythms consists of a group of nerve cells in the brain called the suprachiasmatic nucleus (SCN) which contains about 20,000 nerve cells. It is located in the hypothalamus superior to the optic chiasm and receives direct light information from the retina via the retinohypothalamic tract. The master clock in the brain coordinates all of the body's peripheral clocks through different neural and humoral signals, so they are in synchrony [32].

The nonstop 24/7 lifestyle has given rise to human clock gene mutation, for which the human biological clock does not have a suitable design for physiological adaptation; this leads to an imbalance of autonomic nervous system function toward the parasympathetic predominance in the abdominal compartment and the sympathetic predominance in the muscular and thoracic compartments, resulting in the impairment of insulin secretion, glucose uptake by the muscle, and increase in blood pressure, intra-abdominal fat, and fatty liver [33].

The timing and nutritional composition of meals can regulate circadian rhythms, particularly in the peripheral tissue. The translation of these findings to human physiology now represents an important goal. In healthy humans, glucose tolerance lowers throughout the day, leading to the term “afternoon diabetes”; a daily rhythm in pancreatic insulin production is observed, with increased insulin production in the morning compared to the evening. Moreover, lipid metabolism exhibits circadian regulation, with elevated plasma concentrations of triacylglycerol during the biological night and an elevated postprandial response following a nighttime meal compared with the same meal consumed during the day [34]. In 2006, Staels stated “When the clock stops ticking, metabolic syndrome explodes” [35]. When to eat is as important as what to eat.

2.5.1 Sleep in relation to melatonin and growth hormone secretions

Melatonin is synthesized by multiple tissues in the body, but the pineal gland is the major contributor to circulating melatonin concentration. The rhythmic activity of the SCN determines the release of melatonin, which directly correlates with day length, and it may in turn modulate other physiological functions through paracrine signaling. Pancreatic hormone insulin, gastric hormone ghrelin, growth hormone (GH) from the pituitary gland, and leptin hormone represent as key factors in metabolic regulation, and now several circadian factors are recognized as regulators of their secretion and activity. Sleep deprivation results in circadian misalignment and increases markers of inflammation and IR. A better understanding of such relationships might prove useful and supportive in designing new therapeutic approaches for metabolic syndrome [36].

Growth hormone is a peptide hormone secreted by the anterior pituitary under control of the hypothalamic-pituitary axis. Actions of GH depend on the age of the individual. The primary role of GH in children and adolescents is to promote growth until the final adult height is achieved, while in adults, the role of GH is the regulation of protein, carbohydrate, and lipid metabolism, insulin resistance, and metabolic homeostasis. Sleep restriction and disturbance have also been shown to negatively impact hormone secretion. In sleep deprivation cases, GH secretion decreases, the appetite-suppressing hormone leptin decreases, and the appetite-stimulating hormone ghrelin increases. The end result is the consumption of additional food and calories. Plasma GH peak appeared with the onset of deep sleep and did not correlate with the changes in plasma glucose and insulin. GH secretion decreased if the onset of sleep was delayed [37].

2.6 Risk assessment

Metabolic syndrome directly promotes the development of atherosclerotic cardiovascular disease (ASCVD) [38] and type II diabetes mellitus [39]. Atherogenic dyslipidemia, high circulating levels of prothrombotic factors, and the increase of inflammatory markers carry a higher risk for acute cardiovascular syndromes [40]. Previous studies on middle-aged persons with metabolic syndrome had concluded that many middle-aged people are at increased absolute risk for cardiovascular diseases in the 10-year risk. Furthermore, in young adults who develop the syndrome, long-term risk for ASCVD is increased even when the 10-year risk is not high. The Framingham risk scoring is used to classify metabolic syndrome patients into three risk categories based on a 10-year risk for coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure risk: *low-risk* (10-year risk <10%), *moderate-risk* (10-year risk 10–20%), and *high-risk patients* (10-year risk >20%) [41, 42].

3. Metabolic syndrome, mental and cognitive functions

Obesity and dementia frequently coexist. They share many common pathways such as insulin resistance as well as inflammation and oxidative stress. Midlife obesity is directly related to the risk of developing dementia later in life. Dementia is a syndrome characterized by gradual decline in cognitive functions (memory, attention, behavior, language, mood, and learning). In 2008, Dr. Suzanne de la Monte and Dr. Jack Wands proposed that Alzheimer's disease could be termed type III diabetes, based on the fact that IR within the brain revealed to be a characteristic of Alzheimer's disease [43]. There is no definite cure for dementia, and prevention

is the only option. Prevention may be achieved by early treatment of the risk factors resulting in cognitive impairments (obesity, DM, HTN, smoking, dyslipidemia, anxiety, and depression). Several biomarkers could be involved in the pathogenesis of mild cognitive impairment or early neurodegenerative diseases. Assessment of these biomarkers in obese middle-aged persons could serve as a basis for early management to alleviate the burden of cognitive impairment and dementia in the future.

3.1 Cognitive and mental evaluations

The Mini-Mental State Examination (MMSE) was performed for clinical evaluation of mental and cognitive status. The 30-point questionnaires take between 5 and 10 minutes and examination functions including registration, attention, calculation, recall, language, commands, and orientation [44]. It is a sensitive, valid, and reliable method that is used extensively in clinical and research settings to measure cognitive impairment and to estimate the severity and progression of cognitive impairment. It is also used to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. Sleep quality and the number of sleep hours and their pattern were evaluated. Exposure to sun and length of time, duration, and clothing were recorded. General subjective life stresses, life pattern to evaluate general activity, and history of exercising were recorded.

C-peptide was detected by C-peptide enzyme immunoassay [45]. Modified homeostatic model assessment of insulin resistance (M.HOMA-IR) was calculated by Eq. (1), in which insulin was replaced by C-peptide so as to be applied on diabetic patients using exogenous insulin [46]:

$$\text{M.HOMA - IR} = 1.5 + \text{Fasting blood glucose} \times \text{Fasting c - peptide} / 2800 \quad (1)$$

Blood sampling and biochemical markers of cognitive function impairments were performed as ceramide kinase enzyme, alpha-synuclein, serum clusterin, amyloid beta, and inflammatory markers (hs-CRP, IL-6, and TNF- α).

Ceramides are agents involved in the pathogenesis of mild cognitive impairment or early neurodegenerative diseases. They are mediated by insulin resistance and inflammatory states. Ceramides are lipid soluble and therefore likely to readily cross the blood-brain barrier resulting in cytotoxic effects in the central nervous system with various dementia-associated diseases, including Alzheimer's disease. It is important to prevent its elevation in the human body via increasing the activity of the ceramide kinase enzyme (CERK enzyme) that converts the ceramide to ceramide-1-phosphate (C1P) via its phosphorylation. C1P is a sphingolipid metabolite that has been implicated in the membrane fusion of brain synaptic vesicles and neutrophil phagolysosome formation. C1P is a key regulator of cell growth and survival, it stimulates DNA synthesis and cell division, and it is a potent inhibitor of apoptosis. Many studies have shown that C1P is important for membrane biology and for the regulation of membrane-bound proteins and the CERK enzyme has appeared to be tightly regulated in order to control both ceramide levels and production of C1P [47]. Improvement of the metabolic profiles including C-peptide concentration and the M.HOMA-IR values was associated with the improvement of the serum level of the enzyme CERK and of cognitive functions [48].

Alpha-synuclein (α -Syn) protein was originally isolated from Alzheimer's disease plaques and was thought to be a presynaptic nerve terminal protein. The α -Syn is a member of the synuclein's family of cytoplasmic, predominantly neuron-specific proteins. Synucleins are small, prone to aggregate proteins associated

with several neurodegenerative diseases. The α -Syn has been found in body fluids, including blood and cerebrospinal fluid, peripheral tissues, and the central nervous system. Previous reports suggest that α -Syn is widely expressed peripherally, including the macrophages. The expression of α -Syn is enhanced in activated macrophages, suggesting that α -Syn may modulate macrophage function and thereby inflammatory processes. Diet-induced obesity may be an environmental risk factor for the development of α -synucleinopathies [49]. There was a significant positive correlation between serum IL-6 and serum α -Syn. Fighting obesity, dyslipidemia, and the associated complications especially the inflammatory processes improved the deleterious effects on the cognitive functions in obese persons [50].

Clusterin (apolipoprotein J) is a heterodimeric glycoprotein in which α and β chains are interconnected via five disulfide bonds. There is a strong association between the single-nucleotide polymorphisms in the clusterin gene and Alzheimer's disease. Moreover, plasma clusterin is considered a potential peripheral biomarker of cognitive dysfunction and AD. Clusterin may be related to AD pathogenesis through various mechanisms. It could bind amyloid extracellularly and inhibit the aggregation of amyloid beta monomers into toxic oligomers. In addition, the neurotoxicity of the amyloid might be reduced by the interaction of clusterin with the molecules involved in signal transduction, DNA repair, cell cycle, and apoptosis. Brain apolipoprotein clusterin plays an important role in cholesterol transport and neuronal lipid metabolism. Furthermore, it has a role in the inhibition of neuroinflammation which is thought to be a major factor in AD pathogenesis and identified as a key component in cerebrovascular diseases. In addition, it is known that neuroinflammation plays an important role in dementia pathogenesis and neurodegenerative diseases [51, 52]. The improvement of the C-peptide concentration and the M.HOMA values were parallel with improvement of oral cognitive tests and clusterin value; clusterin was presented as a cognitive function parameter [52].

Plasma amyloid beta ($A\beta$) can be applied as trait, risk, or state biomarker for AD and denote a neuropathologic condition. A previous study has reported the presence of a stronger correlation between plasma $A\beta$ and positron emission tomography or Pittsburgh Compound-B-C11 as radiotracers illustrate fibrillar brain amyloid deposits which is a reliable method to measure brain amyloid plaque accumulation. Reduction of body weight and improving the metabolic profile reduced the level of serum $A\beta$ protein, an effective role in improving the cognitive function. At the same time, previous studies stated that plasma $A\beta$ measures possibly aid in clinical investigations as markers for the pharmacological impacts of medications that influence amyloid protein transformation [53].

Serum hs-CRP level may be used as a marker for cognitive functions in obese middle-aged persons. Peripheral inflammatory markers are elevated in obese patients. Improvement in cognitive functions is recorded after dietary therapy, with decrease in hs-CRP serum levels. Significant inverse correlation is found between cognitive functions and hs-CRP levels, insulin resistance, minimal waist circumference, and BMI [54].

4. Management of metabolic syndrome

As the presence of MetS carries a risk for cardiovascular diseases and diabetes mellitus, the primary goal of clinical management to individuals with metabolic syndrome is directed towards decreasing the major metabolic risk factors: high LDL-C, hypertension, obesity by losing fat percentage and not muscle mass, decreasing insulin resistance, blood glucose, and maintaining normal HDL and

triglyceride levels through lifestyle changes. Moreover, medical drug therapy might be considered in high-risk patients to modify cardiovascular disease risk factors [7]. Bariatric surgery has been indicated to treat morbidly obese persons. The safety and effectiveness of bariatric surgery in patients with metabolic syndrome have been studied and encouraged [55, 56].

Chronotherapy means the timing of drug and dietary treatment to obtain maximum therapeutic effect. It can be achieved through the timing of light exposure, exercise, food consumption, medication uptake, and sleep, with the goal of optimizing any treatment by taking into account the circadian rhythms of the body [57].

4.1 Therapeutic lifestyle modifications

Physical exercise, diet, and adequate sleep are the way to reach the target. Gradual permanent change in the patient's lifestyle can lead to better and easily maintain normal parameters than major food deprivation introduced all at once. Implementing the following changes increases the chances of success: changing a sedentary life through regular sustained physical exercise and eating several small portions of different foods varieties; consuming complex carbohydrates such as barley, oat, corn, quinoa, and brown rice while decreasing the consumption of simple carbohydrates such as white sugar and sweets; eating fresh seasonal fruit and vegetables daily as they are good sources of fiber, vitamins, and minerals noting that dietary fiber helps prevent gastrointestinal problems such as flatulence and constipation; eating foods rich in unsaturated fatty acids such as salmon, mackerel, sardines, tuna, raw nuts, and flaxseed oil; increasing the consumption of black beans, kidney beans, green peas, and lentils; avoiding processed and red meats; limiting the intake of sugar, salt, and carbonated drinks; replacing salt with spices; boiling, baking, or steaming food instead of frying; paying attention to portion size by utilizing smaller plates; and drinking plenty of fluids, of which 30 ml/kg/day water is the best [7].

Avoid light exposure in late evening or at night as artificial light disrupts the circadian rhythm and the production of melatonin and therefore has a negative effect on sleep quality, mood, cognition, and hormonal functions [58, 59]. Sleep early and get at least 6 hours of sleep per night [60], and stop smoking.

4.2 Energy-restricted diets

For our patients, the Harris-Benedict equation (Eq. (2)) was used to calculate the caloric requirements for each individual in order to estimate the caloric needs or basal energy expenditure (BEE) as follows [61]:

$$\begin{aligned} \text{Males: BEE} &= 66.5 + 13.8 (\text{weight in Kg}) + 5 (\text{height in cm}) - 6.8 (\text{age}). \\ \text{Females: BEE} &= 65.5 + 9.6 (\text{weight in Kg}) + 1.7 (\text{height in cm}) - 4.7 (\text{age}). \end{aligned} \quad (2)$$

These equations yield basal energy expenditure that is frequently multiplied by various activities and/or stress factors to generate the patient's estimated resting energy expenditure, and then we subtracted 500 calories per week from the calculated energy requirement, to produce weight loss of 0.5–1 kg per week. A hypocaloric diet goal is to reduce body weight by about 10% over the first 6 months. The menu varied according to the participant's age and eating habits. It was low in fat (20–25%), high in complex carbohydrate (50–60%), and sufficient in protein (25–30%) from both animal and vegetarian sources [54]. Carbohydrates in the

form of complex CHO, which have low glycemic loads and indexes such as whole grains, oats, fresh seasonal fruits, and vegetables, were consumed to increase high fiber content (eight servings of fresh vegetables and fruits/day). On the other hand, they were instructed to decrease foods rich in saturated fats such as fried foods and packaged meats [62].

4.3 The Mediterranean diet

The Mediterranean diet (MedDiet) is based on scientific evidence that inhabitants of Mediterranean countries (Greece, Italy, and Spain), around the Mediterranean Sea adhering to the principles of nutrition traditional for their region, have better health indicators than people in other areas. Originally, it was developed to prevent and treat the symptoms of hypertension and/or heart disease. In this MedDiet, the emphasis is on the use of plant-based foods as the main source of nourishment: fruits, vegetables, cereals, nuts, legumes, seeds, and whole grains. It is also recommended to replace butter and hydrogenated fats with extra-virgin olive oil and salts with spices and herbs. Red meat and sweets should be eaten once a week, and the main sources of protein should be eggs, yoghurt, fish, and poultry. Red wine could be taken in limited amounts (one glass per day for women; two glasses per day for men) [63–65].

4.4 Role of functional foods

There is no universal definition for functional foods, but the easiest one is from the International Food Information Council which described functional foods as “dietary or food components that provide a health benefit beyond providing basic nutrition” [55]. Functional foods have an important role in the management of metabolic syndrome. Functional foods can help in weight loss, regulation of blood pressure, and control of blood glucose and lipid profile levels. Previous studies supported the beneficial effects of using functional foods containing bioactive components in the management of metabolic syndrome. This includes the intake of foods which have a thermogenesis effect (process in which body heat production increases, e.g., ginger, caffeine, red pepper, and green tea); functional foods with anti-inflammatory properties such as curcumin; and foods with the ability to increase insulin sensitivity, e.g., cinnamon, and increase intake of foods rich in plant estrogens such as soymilk, soybeans, flaxseed, sesame, green beans, fennel, peanut, and pumpkin seeds. In addition, soy products are rich in amino acids and can preserve lean body mass, decrease body fat percentage, and increase basal metabolic rate [48, 50, 53, 66–70].

4.4.1 Functional food classification

- Natural functional foods: food products rich in biological active compounds (food rich in dietary fiber such as oat, barley, psyllium, vegetables, and fruits) [66]
- Foods with approved scientific health nutrients: apple (pectin), garlic (*Allium sativum*), and fish (omega 3 fatty acids) [71]
- Fortified foods with specific nutrients: iron fortified chocolate for iron deficiency anemia, calcium fortified juices, and zinc fortified products
- Fermented products rich in probiotics or synbiotics [72]

4.4.2 Eat to beat metabolic syndrome

The use of functional and prepared designed food would help fight MetS. Three thousand years ago, Hippocrates announced the tenet “Let food be thy medicine and medicine be thy food.” Dietary supplements proved to improve the MetS criteria which include Syrian bread prepared mainly from barley flour and wheat germ mixed with either turmeric or ginger; doum biscuits; barley biscuits; bread prepared with soybean flour and enriched with curcumin or ginger; and cookies prepared with whole wheat flour and fennel or chia seeds. The higher fiber content of these products has a satiety effect so as to decrease food consumption. Moreover, fibers decrease digestion and absorption of dietary carbohydrates. Soy flour is a very rich source of essential amino acids except methionine. Preparation of bakery products using bioactive ingredients has positive beneficial effects for obesity, diabetes, and dyslipidemia management. These compounds have different benefits such as anti-atherogenic, antioxidant, and anti-inflammatory effects [48, 50, 53, 67–70].

4.5 Pharmacological management

There are no specific recommendations regarding the pharmacological management of metabolic syndrome; instead, the focus is on the management of the risk factors which need to be aggressively treated in order to prevent cardiovascular disease and type II diabetes mellitus if lifestyle changes aren't enough to reduce the risks. The available evidence of the pharmacological prescriptions is related to their cardiovascular benefits in clinical practice. Pharmacological treatments include statins and/or fibrates for dyslipidemia, angiotensin-converting enzyme inhibitors or renin-angiotensin-aldosterone system inhibitors for hypertension, metformin or sodium/glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1RAs) for glucose intolerance, and low-dose aspirin for prevention of arterial thrombosis [73]. Melatonin provides an innovative approach in the management of MetS through its useful effects on circadian rhythmicity, insulin resistance, dyslipidemia, high blood pressure, weight loss, and improving the antioxidative status (melatonin tablet 1 mg/kg) [74, 75]. Melatonin reduces the toxicity of many pharmaceutical agents and has a high safety profile [76].

5. Conclusion

Prevention is the best form of treatment of metabolic syndrome, and it starts from childhood by following a healthy lifestyle based on proper nutrition, exercise, and adequate early night sleep. Timing of food consumption, food quality, food quantity, light exposure, medication intake, and sleep are likely to play an important role in human health. Eat small portion sizes of food, and follow the rhythm of the day to maintain the synchronicity of the biological clock. Consuming natural effective supplements rich in bioactive substances leads toward the optimization of biochemical parameters of patients with metabolic syndrome in favor of a healthy outcome. Bariatric surgery should be considered in individuals with morbid obesity or obesity associated with comorbidity.

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Abbreviations

ASCVD	atherosclerotic cardiovascular disease
α-Syn	alpha-synuclein
AD	Alzheimer’s disease
Aβ	amyloid beta
BEE	basal energy expenditure
BMI	body mass index
C1P	ceramide-1-phosphate
CERK	ceramide kinase enzyme
CRP	C-reactive protein
DBP	diastolic blood pressure
DM	diabetes mellitus
GLP-1RAs	glucagon-like peptide 1 receptor agonists
GH	growth hormone
HDL-c	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
IL-10	interleukin-10
IR	insulin resistance
LDL-c	low-density lipoprotein cholesterol
MedDiet	Mediterranean diet
MetS	metabolic syndrome
M.HOMA-IR	modified homeostatic model assessment of insulin resistance
MMSE	mini-mental state examination
SBP	systolic blood pressure
SCN	suprachiasmatic nucleus
TG	triglycerides
TNF-α	tumor necrosis factor-α
WC	waist circumference

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